

VI. Summary of Benefits, Risks of the Proposed Formulation

In a very brief summation (Volume 216, pages 489-92), the applicant states that the irritable bowel syndrome (IBS) is a common problem, estimated to affect 10-15% of the population, and 70-75% of those with IBS are women. They further state that 70% of the patients enrolled in the two large Phase III studies were classified as having the diarrhea-predominant form of IBS, and that in women with non-constipated IBS no therapeutic agent has been proved effective in relieving the most bothersome IBS symptoms of IBS-related abdominal pain, urgency and increased stool frequency. Even the few agents approved for treatment of IBS symptoms are labeled as "adjunctive" treatment or as "possibly" effective, and that these agents were introduced before regulatory standards were put into place that required substantial evidence of effectiveness before approval. These points are taken to indicate an unmet need for new therapy.

Comment: Much of what is claimed above is true, which is why this application was granted accelerated review. However, it does not seem correct to say that 70% of women with IBS have the "diarrhea-predominant" form of IBS, based on recruitment into the studies S3BA3001 and S3BA3002, whose protocols required selection of IBS patients to avoid those with hard stools.

The applicant further states that they have carried out two large, identically designed and almost simultaneous, adequate and well controlled Phase III studies of alosetron as a novel pharmacologic treatment that showed consistent benefit for the most bothersome symptoms of IBS in women with diarrhea-predominant forms of the disorder throughout the treatment period of 12 weeks, with return of symptoms when treatment was stopped. The applicant points out that 3670 patients and healthy volunteers enrolled in 52 studies worldwide have contributed to the efficacy and safety conclusions, including 1810 patients with IBS who have been treated with alosetron alone. The final summary statement (Section 8.11.6, Volume 216, page 492) states:

"In comparison to existing therapies, alosetron represents a significant improvement for the treatment of females with diarrhea-predominant IBS. Alosetron provides robust efficacy in relieving the most bothersome IBS symptoms: pain, urgency to defecate, and frequency of stooling. The compelling evidence of effectiveness combined with a very favorable safety profile provides persuasive evidence for alosetron as a therapeutic advance and a first-line monotherapy for the significant population of females with diarrhea-predominant IBS patients." [sic: did they mean patients or symptoms?]

With respect to the safety of alosetron, the applicant claims that alosetron is "well tolerated in the treatment of females with diarrhea-predominant IBS," and that the "extensive non-clinical and clinical database confirms an excellent safety profile across all populations studied." In the Phase II and III studies, constipation was the only adverse event occurring at substantially higher frequency in alosetron-treated patients, in comparison to those receiving placebo." They further state that "If constipation occurred, it tended to do so within the first month of therapy," and was transient in the majority of cases, and that a third of the patients who reported constipated withdrew from the study. Therefore the majority of subjects who reported constipation continued to derive benefit from alosetron therapy, since comparable relief was reported by constipated or non-constipated subjects. Finally, they state that "No other adverse event, serious adverse event, or laboratory values were noteworthy during the alosetron clinical development program."

Comment: It is very disturbing that the applicant has chosen to downplay so strongly the important issue of constipation induced commonly and predictably by alosetron, and has totally ignored the potentially very serious although uncommon problems of ischemic colitis and perhaps rare alosetron-induced hepatitis with both serum transaminase and bilirubin elevations.

The applicant has a duty to recognize, admit, and publicize the constipation problem, and to investigate it much more thoroughly in analysis of the excellent data gathered in the studies carried out. The daily telephone data entry system was an innovative contribution to the field of clinical investigation of this functional bowel disorder, as was the development of consensus on what patients and their physicians wanted from treatment, the "adequate relief of IBS-related pain and discomfort" and the bothersome symptoms of urgency and excessive stool frequency. In the further analysis of the constipation problem, clear distinction should be made between the physicians' classification of what type of IBS the patients had, based on histories taken at screening or entry, and the data on stool characteristics and frequency gathered during the two-week screening period that were not available to the investigators. These need to be compared and contrasted and explained. Further attention should be paid to the program of the 4-day interruption of treatment if constipation occurred. There may be an important clue in that data that could illuminate the question of how the alosetron regimen might be adjusted for each of the individual patients, perhaps not taking 1 mg. b.i.d. every day continuously, but maybe once daily, or intermittently, to avoid constipation yet obtain relief of pain/discomfort and the other symptoms. This will have to be dealt with in the labeling, in the instructions to physicians and patients as to how best to use this new agent, and in the advertising and promotion of the product if it is approved for prescribed clinical use and marketing.

The serious clinical adverse event of ischemic colitis cannot be ignored. It must be dealt with constructively and thoroughly. Although only 3 cases out of 921 patients (91 men, 830 women) exposed were diagnosed, preliminary inspection of the adverse events reported in the first interim report of the year-long study S3BA3003 indicates that there were several cases in the alosetron-treated patients of unexplained and uninvestigated rectal bleeding. This issue will be explored further in the upcoming safety review of the second interim report of that study just received on 27 September, and the review of the 4-month safety update received at the same time. It will be important to re-examine the adverse events of the 12-week studies of dose-ranging and clinical efficacy of 1 mg b.i.d. in women to see if other cases of unexplained rectal bleeding may be identified. We requested this of the sponsor at the meeting held last week on 6 October 1999.

Ischemic colitis caused by drugs may be mild and transient if no occlusion of major mesenteric vessels occurs, but can be catastrophic if it does, resulting in bowel infarction, segmental gangrene, perforation, peritonitis, and death if the dead bowel is not resected in time. Such problems might be anticipated to occur rarely, in patients predisposed by underlying vascular disease or circulatory events such as hypotension or cardiac failure. On the other hand, there may be milder cases of slight ischemic colitis that are not recognized or diagnosed, not investigated, not treated. The index of suspicion among physicians and patients needs to be raised to deal with this uncommon but potentially very serious adverse effect of alosetron. The calculated 95% confidence interval for the true incidence of ischemic colitis (Graham, 1999) has an upper bound between 1 and 2% of women with IBS taking alosetron at a dose of 1 mg b.i.d. for 12 weeks, based on the three cases discovered. It is not yet known whether the risk of ischemic colitis diminishes after the first few months on treatment, or continues at some continued hazard rate beyond the period of well studied treatment, 12 weeks. The further analyses of S3BA3003 data, and of data from other trials, may help illuminate this point.

The single case of apparent alosetron-induced hepatitis in patient #4595 in S3BA3001 may be just that—a single case, or it may be the first of more to come. No other cases of combined serum ALT and total bilirubin increase were detected in the other major trials of dose-ranging or efficacy (S3BP12, S3BA2001; S3BA3002), but the first interim report of the year-long study S3BA3003 omitted any data on serum activities of liver enzymes and concentration of bilirubin, while including results of blood counts and serum electrolytes and other chemical concentrations. We shall look again in the review of the second interim report, and request additional information from the applicant on the point.

It is this reviewer's opinion that, if alosetron is approved for marketing, a prospective study of a sufficient cohort of patients starting treatment with alosetron should be observed on treatment to detect and investigate cases of rectal bleeding, to improve our estimate of its true incidence, obtain information on risk factors, and other useful information pertinent to ischemic colitis. The study should be designed to be large enough to provide significant data and perhaps large enough to detect ALT rises (with appropriate follow-up and further study) as well. Design of the study will be very important, and commitment to initiate it promptly is another key consideration. A major question may be whether to include a control group, using an approved anti-diarrheal agent such as loperamide, and a set of rules for adjusting treatment regimens for individuals with both agents.

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VII. Regulatory Recommendations

Based on review of the safety data of this submission for marketing of alosetron hydrochloride (LOTIRONEX®, Glaxo Wellcome) for treatment of women with diarrhea-predominant forms of IBS, the following recommendations are made:


1. The frequent problem of alosetron-induced constipation must be recognized much more clearly by Glaxo Wellcome, and the labeling revised to recognize it. Further, precautions to be taken when prescribing alosetron should be specified, and instructions written as to how the problem of constipation should be handled by adjustment of the treatment regimen.
2. The infrequent but serious problem of alosetron-induced ischemic colitis must also be much more clearly recognized and addressed in the labeling, including a warning to physicians that it may occur with an incidence of about 1:300 patients
3. The rare but also potentially serious problem of alosetron-induced hepatitis, or idiosyncratic hepatotoxicity, must be recognized and addressed in revised labeling.
4. A post-marketing prospective study of sufficient patients on the approved regimen of alosetron 1 mg b.i.d. should be a condition for approval. The study should be powered to detect ischemic colitis and possible hepatotoxicity and provide better data to establish their true incidence, as well as to learn about predisposing factors. Ideally the study should be controlled with a reasonably safe agent such as loperamide (IMODIUM®, Janssen) 2 mg capsules as labeled for treatment of diarrhea.
5. The term "diarrhea-predominant" as a defining subtype of the IBS patients is probably not appropriate, and should be called "non-constipated" IBS to emphasize the concern that the drug should not be given to constipated patients, and may produce constipation frequently if given to patients with IBS who are not constipated previously.

It is clear that a number of other issues have been raised from this safety review of the submitted data, from which a number of suggestions have emerged. We suggest that the applicant firm:

- i. Carry out selected pharmacodynamic studies of esophageal, gastric, small bowel and colonic motility using the *1 mg b.i.d. dose and regimen of alosetron in women with IBS*, basing the study sizes for significance on the previously obtained data for men, healthy subjects, and higher alosetron doses;
- ii. Develop a format for displaying all of the telephone data for an individual patient on a single sheet, if possible, for inclusion with the case report forms;
- iii. Specify a more consistent process for categorizing IBS into constipation-predominant, diarrhea-predominant, or alternating forms, and correlate those categories with data from the daily telephone entry system;
- iv. Consider initiating additional studies of effects of alosetron, and comparable agents, on the microvasculature of and circulation to the colon, perhaps using suitable animal models;
- v. Investigate further and seek to understand and explain the gender effect, its mechanisms and other characteristics;

- vi. Allow use of their data on ischemic colitis for preparation of an abstract to be submitted for the upcoming Digestive Disease Week meetings in May 2000, and for writing a manuscript for publication in a leading peer-reviewed journal in the field of gastroenterology to be submitted at about that same time;
- vii. Include in future clinical protocols the instruction to patients, investigators, and study coordinators at all sites that withdrawal from study is permitted but good reason should be given and follow-up will expected off study treatment until the end of the planned study period. Vague and non-specific "reasons" such a consent withdrawn, lost to follow-up, did not return, refused medication, etc. will not be considerable acceptable.

The applicant is commended for carrying out these well controlled studies and for introducing new and effective methods for gathering valid data from patients.

 22 Oct 1999
John R. Senior, M.D., Medical Officer date
Division of Gastrointestinal & Coagulation Drug Products

cc:

NDA 21-107

HFD-180

HFD-180/LTalarico

HFD-180/SAurecchia

HFD-180/HGallo-Torres

HFD-180/RPrizont

HFD-180/JSenior

HFD-180/JChoudary

Hfd-180/KZhang

HFD-180/EDuffy

HFD-180/MYsern

HFD-870/DLee

HFD-870/RKavanagh

HFD-720/PFlyer

HFD-715/DHoberman


HFD-733/DGrzham

HFD-181/PLevine

f/t 10/22/99 jgw

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Concur. October 25, 1999

 *Hugo E. Gallo-Torres, M.D., Ph.D.*

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M E M O R A N D U M

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: November 17, 1999

FROM: Medical Team Leader (MTL)
Division of Gastrointestinal and Coagulation Drug Products, (HFD-180)

SUBJECT: LOTRONEXTM (alosetron hydrochloride; GR68755), NDA 21-107:
Secondary, Multidisciplinary Review and Recommendations for
Regulatory Action

TO: Director
Office of Drug Evaluation III, HFD-103

THROUGH: Director, Division of Gastrointestinal and Coagulation
Drug Products, (HFD-180)

SYNOPSIS

From this secondary review, a recommendation for Regulatory Action is formulated on the basis of a multidisciplinary approach which considers the contribution of each and all primary reviewers involved with NDA 21,107, LOTRONEXTM, alosetron hydrochloride, GR68755.

GlaxoWellcome (the applicant, sponsor) proposes oral tablets, administered twice-a-day for up to 12 weeks, with or without food, for treating irritable bowel syndrome (IBS) in women over 17 years of age whose predominant bowel symptom is diarrhea, either alone or as part of an alternating pattern. Alosetron is a 5-hydroxytryptamine Type 3 (5-HT₃) receptor antagonist. Three 5-HT₃ receptor antagonists are currently approved for the prevention/treatment of emesis induced by cancer chemotherapy or preoperatively: ondansetron (ZOFTRAN[®]), granisetron (KYTRIL[®]) and dolasetron (ANZEMET[®]). For the approved indications, the 5-HT₃ R. Ant. are used short-term but are generally perceived as safe (and effective). Adverse events most often reported with these approved 5-HT₃R Ant. are headache and constipation. It is, of course understood, that the proposed indication "treatment of IBS," requires the use of alosetron for longer periods of time (3 months) and this makes it necessary a very detailed review of the safety information provided by the sponsor.

As summarized in Section I, IBS is a common problem, usually diagnosed by exclusion, that affects more women than men. In this era of managed care, in the case of IBS, a minimal evaluation and a therapeutic trial, rather than extensive investigation, is emphasized.

In Section II, a summary of the evidence presented by the sponsor is given. All questions regarding Chemistry and raised by M. Ysern, have been promptly addressed by the sponsor. No issues of concern have been identified by Dr. K. Zhang, the Pharm/Tox reviewer. Transient decreases in acute hearing were observed in RH rats and beagle dogs after 12-month oral administration of >1000 fold the recommended dose of alosetron; but no effect on hearing was noted after 102-week administration of the drug to Wistar rats. Alosetron did not have secondary effects on the cardiovascular system or electrophysiologic effects on the heart. The human PK/PD data appear incomplete. The Clinical/Statistical data consisted of two Phase II dose-ranging trials that showed that efficacy was preferentially observed in females and that 1 mg b.i.d. is the optimal clinical dose. After an end-of-Phase II meeting with the Division, the sponsor elected to include only women in Phase III trials. The main evidence of efficacy consists of two adequate and well-designed 12-week trials comparing alosetron 1 mg b.i.d. to placebo. The primary endpoint of efficacy in these principal trials was adequate relief of IBS pain and discomfort, an adequate endpoint of evaluation. Secondary endpoints of efficacy included changes in stool consistence, stool frequency, urgency, % days with incomplete evacuation and bloating. The weekly data were captured electronically, thus providing more accurate information than the use of the customary unreliable diaries. The procedures to assess safety were adequate.

In section III the justification for accelerated review of this application is summarized. NDA 21-107 was granted accelerated review because of the lack of effective treatment for IBS. At present, there is no "gold standard" treatment for IBS, especially for non-constipated females with IBS. No agent has been shown to be of proven benefit in the treatment of the patient's most bothersome symptoms of abdominal pain, urgency and increased stool frequency. Alosetron appears to be suitable to meet this need.

As summarized in Section IV, reviews started in July, 1999. The review of the clinical data of efficacy was performed by Dr. Prizont. The safety review was performed by Dr. Senior. The NDA was presented to the GI Advisory Committee Meeting on November 16, 1999.

Summary Review of the evidence presented by the sponsor is given in Section V. The primary endpoint of efficacy, adequate relief of IBS pain and discomfort, showed 10 to 15% therapeutic gain as well as similar improvement of stool frequency, stool consistency and urgency in one trial. All these findings were replicated in the other critical trial. At the time of randomization into the trials, the female patients did not fulfill the definition of diarrhea. Efficacy was shown in the ITT and "diarrhea prominent"- IBS group. However, alosetron was not differentiated from placebo in the diarrhea/constipation alternating group. This information will be incorporated into the alosetron labeling.

The major AE was constipation, occurring in 26% to 30% of patients at the alosetron dose of 1 mg b.i.d., significantly greater than the 5% of patients on placebo. The constipation was dose-related and was the most frequent cause for patients to withdraw

from the trials. In his safety review as well as his presentation to the GI Advisory Committee, Dr. Senior addressed further characterization of constipation and this information should be incorporated into the labeling. There were no changes of concern in laboratory values, except for mild but transient transaminitis and mild elevation of bilirubin without overt jaundice experienced by one patient. Again, this information should, conservatively, be incorporated into the labeling.

Four alosetron-treated patients, each participating in a separate randomized clinical trial, experienced episodes of ischemic/infectious colitis. The ischemic colitis cases in the alosetron safety database are discussed next in detail in this review¹ with the clinical summaries and pathology assessment.² A strong case is made that, although ad hoc histologic interpretation can provide significant information, it should **never replace the careful clinical judgment**. All four patients had a clinical syndrome of ischemic colitis and this clinical impression was **consistently confirmed** by endoscopic examinations. This ischemic colitis may coexist or predispose to, or even be the consequence of, some form of E. coli infection. There is no clear cut evidence for a causal relationship between alosetron treatment and the development of this colitis, which appears to be acute and self-limiting. In an IBS patient with diarrhea and bloody stools, the most important question is whether the clinical picture represents the first episode of chronic inflammatory bowel disease (ulcerative colitis or Crohn's disease) or acute self-limited colitis (acute infectious-type colitis, often caused by Campylobacter, Salmonella, or Shigella). All four cases of colitis resolved without sequelae. There were no instances of necrosis/perforation that may necessitate colectomy. On the other hand, the direct or indirect contribution of alosetron use to the complex clinical/endoscopic/histopathological picture in these four patients cannot be eliminated with certainty, since none was seen among those patients taking placebo. The occurrence of colitis should be carefully and conservatively addressed in the labeling.

This reviewer agrees with Dr. Kavagh, the Biopharm. Reviewer. Further PK and PD studies and evaluations, effects on motility of the colon, whole gastrointestinal tract, stomach, esophageal motility, effects on lower esophageal sphincter pressure, of the 1mg b.i.d. proposed dose should be carried out.

The status and expected contribution to the formulation of a Regulatory Action on NDA 21-107 of the clinical Report of Study 3003 are carefully considered in Section VI.

Recommendations for Regulatory Action are provided in Section VII of this review. Therapeutic gain was clearly demonstrated by alosetron using the primary and three of the five secondary efficacy endpoints of evaluation. The therapeutic gain in comparison to placebo is not very great, but clear cut differentiation from this negative comparator was shown and the results of one principal trial were clearly replicated in the other. Some of the encountered AEs, such as constipation and headaches were expected since they

¹ [T.T. Nostrant, et al. Histopathology differentiates acute self-limited colitis from ulcerative colitis. *Gastroenterology* 92:318-328 (1978)]

² [C.M. Surawicz and L. Belic, Rectal biopsy helps distinguish acute self-limited colitis from idiopathic inflammatory bowel disease. *Gastroenterology* 86:104-113 (1984)].

have been observed with the three approved 5-HT₃ receptor antagonists. With alosetron however, there appears to be more (and worse) constipation and less headache than with the other 5-HT₃ receptor antagonists. The three adverse events of concern, constipation, ischemic/infectious colitis and possible liver injury can be - carefully and conservatively- addressed in the labeling. AEs/Evaluations of Special interest which were discussed in detail in this review included preliminary special studies as well as audiometry testing and EKG changes. In humans, no significant differences in either pure tone audiometry results or development of tinnitus between alosetron and comparators were shown. Alosetron treatment did not cause significant EKG abnormalities.

All things considered, alosetron appears to be effective and well tolerated. Since there are no major issues that remain unresolved, this reviewer recommends approval of alosetron for the proposed indication.

It is strongly recommended that commitments to promptly initiate Phase IV PK/PD evaluations and Clinical studies (see separate memorandum by MTL and Division Director), be obtained before approval. These trials should be designed to: a) prospectively characterize unexplained rectal bleeding as possible ischemic colitis, in a large number of IBS patients being administered alosetron at the proposed dose and regimen and b) better characterize the regimen.

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MULTIDISCIPLINARY, SECONDARY REVIEW
OF NDA 21-107 (ALOTRONEXTM; alosetron
Hydrochloride, GR68755)

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